REMARKS

This responds to the Office Action mailed on March 23, 2006, and the references cited therewith.

Claim 23 has been added. As a result, claims 1-5, 7, 9-18 and 20-23 are now pending in this application.

Claim 23 is directed to a proteinoid microsphere made from particular amino acids (i.e., a mixture of aspartic acid, glutamic acid, asparagine, arginine, and serine amino acids). Support of this subject matter can be found throughout the specification and claims as originally filed, for example, and in the Examples (see, e.g., page 27).

Claims 1, 2, 3, 7, 9, 10 and 17 have been amended. Language relating to covalent attachment of the label has been added to claim 1, 2, 7, 9 and 17. Support of this subject matter can be found throughout the specification and claims as originally filed, for example, in the Examples (see, e.g. pages 28-29). The phrase "such that the proteinoid microsphere further comprises a crosslinking agent" has been added to claims 3 and 10. Support of this subject matter can be found throughout the specification and claims as originally filed, for example, at page 7, lines 1-3.

Applicant submits that no new matter has been added to the specification or claims.

§112, Second Paragraph, Rejection of the Claims

Claims 3, 4, 10 and 11 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner alleges that it is unclear whether claim 3 contains a crosslinking agent.

Applicant submits that claim 3 is definite as written but to expedite the prosecution of the claims, Applicant has added the following language to claims 3 and 10: "such that the proteinoid microsphere further comprises a crosslinking agent."

Applicant requests withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

§102 Rejection of the Claims

Claims 1 and 5 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Yen et al. (Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 20: 342-43 (1993) in light of Krauth (U.S. Patent No. 4,954,435). The Examiner has alleged that Yen et al. disclose proteinoid microspheres comprised of a mixture of amino acids that are thermally condensed (citing col. 1, page 342) that are linked with sulforhodamine 101 (fluorophore as shown by Krauth at col. 7, lines 22-25).

Claim 1 is directed to a labeled proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; wherein the label is covalently linked to the proteinoid microsphere; and the proteinoid microsphere is stable in solution.

Applicant reminds the Examiner that a claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. Applicant has understood from the Office Action that Yen et al. is the alleged anticipating reference while Krauth is used by the Examiner merely to assert that sulforhodamine is a fluorophore. Accordingly, the Krauth disclosure will not be discussed further. If Applicant has not understood the Examiner's rejection, clarification is requested.

Yen et al. is limited to disclosure of separate batches of microspheres made from (A) aromatic and acidic amino acids and (B) aromatic, basic and acidic amino acids, where sulforhodamine is merely adsorbed onto the microspheres.

Therefore, Yen et al. fail to disclose at least one element of the claim (covalent attachment of the label). Applicant submits that the present microspheres are designed to be stable in solution. Hence, the disclosure by Yen et al. of mere adsorption of a sulforhodamine moiety onto a microsphere will not yield a stable microsphere and does not anticipate the present invention.

Applicant respectfully requests that this rejection of claims 1 and 5 under 35 U.S.C. § 102(b) be withdrawn.

§103 Rejections of the Claims

To establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Second, the reference(s) must teach or suggest all the claim elements. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed modification and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. See MPEP § 2143.

Lohrmann, Steiner and Kayyem

Claims 1, 2, 5, 7, 9, 12-18, 20-22 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Lohrmann et al. (U.S. Patent 6,193,953) in view of Steiner et al. (U.S. Patent 4,925,673) and Kayyem et al. (U.S. Patent 6, 232, 295).

The Examiner has alleged that Lohrmann discloses protein microparticles that are comprised of chemically synthesized amino acid polymers at col. 5, lines 40-57, and that Lohrmann discloses fluorine or radioactive iodine as a label at col. 15, lines 1-16. The Examiner further alleges that Lohrmann et al. disclose microparticles with a targeting agent such as an antibody at col. 13, lines 17-29. According to the Examiner, Lohrmann does not disclose proteinoid microspheres but this defect is cured by Steiner, which does disclose proteinoid microspheres. Moreover, according to the Examiner, Kayyem et al. disclose polymeric delivery vehicles that are tissue specific and used on MRI applications.

Claim 1 is directed to a labeled proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; wherein the label is covalently linked to the proteinoid microsphere; and the proteinoid microsphere is stable in solution. Each of the other independent claims is also directed to proteinoid microspheres with covalently linked labels.

The Lohrmann disclosure is limited to microparticles made of proteins and, as the Examiner has stated, Lohrmann does not disclose proteinoid microspheres. Specifically, Lohrmann provides no disclosure or teaching whatsoever on proteinoid microspheres made from thermally condensed amino acids.

The Steiner disclosure is limited to disclosure of microspheres that contain pharmacological agents, where the microspheres are explicitly designed to release the pharmacological agent in the blood, target organ or bodily fluid. See Steiner at col. 3, line 49 to col. 4, line 33.

Kayyem et al. is limited to poly-lysine and protein-containing magnetic resonance imaging agent characterized as a "delivery vehicle comprises a polymeric molecule having a net positive charge complexed with another polymeric molecule having a net negative charge" with at least one contrast agent.

First, Applicant submits that the cited references do not teach or suggest all of the present claim elements. In particular, the combination of Lohrmann, Steiner and Kayyem fails to disclose labeled *proteinoid* microspheres comprising a mixture of amino acids that are thermally condensed.

The present *proteinoid* microspheres are comprised of thermally condensed microspheres of amino acids. Such microspheres may be linked by a combination of non-peptidyl and peptidyl bonds. Hence, any teachings on delivery vehicles and microspheres composed of proteins are irrelevant because the chemical and physical properties of such protein microspheres are different from those of the present invention. For example, microspheres made from proteins are held together by standard peptidyl bonds, whereas microspheres made from thermally-condensed amino acids can have a variety of bonds between their side chain moieties as well as their amino and carboxylate moieties. Therefore, the teachings of Lohrmann and Kayyem on protein delivery systems are irrelevant.

Second, Applicant submits that the Steiner reference explicitly focuses on *release* of a *pharmacological agents* rather than *retention* of a *label* in the proteinoid microsphere.

Applicant submits that one of skill in the art would not be motivated to modify or combine the teachings of Lohrmann on stabilized protein microparticles with the teachings or Steiner on unstable proteinoid microspheres for several reasons. First, as described above, there is no evidence of record that the proteinoid microspheres of Steiner have properties similar to the protein microspheres of Lohrmann that would suggest their interchangeability. Specifically, one of skill in the art can find no teaching in Lohrmann that *proteinoid* microspheres can be substituted for the disclosed protein microspheres or that *proteinoid* microspheres would have

any of the same properties that Lohrmann discloses for protein microparticles (e.g., stability). Kayyem does nothing to satisfy this deficiency because Kayyem is limited to teachings on protein delivery systems and provides no disclosure on proteinoid microspheres.

Nor would one of skill in the art have a reasonable expectation of successfully producing Applicant's invention because the combination of references does not disclose that proteinoid microspheres would be sufficiently stable in solution and under a variety of pH and other conditions to retain the integrity of the microsphere and the label. Steiner discloses only unstable proteinoid microspheres that readily release pharmacological agents. Hence, one of skill in the art could not know from Steiner whether stable proteinoid microspheres could be produced.

Neither Lohrmann nor Kayyem cures this defect because nowhere does Lohrmann or Kayyem address how to make stable proteinoid microspheres. Instead, Lohrmann and Kayyem are limited to teachings on proteins.

Moreover, one of skill in the art would not expect that stability of the protein microcapsules would necessarily be found in a proteinoid microsphere because the bonds that are formed upon thermal condensation of amino acids are not necessarily the peptidyl (-NH-CO-) bonds that are present in proteins. Therefore, one of skill in the art could not reasonably expect that simple substitution of the proteinoid microspheres of Steiner for the protein microcapsules of Lohrmann would successfully generate the present invention.

Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953), Steiner (U.S. Patent No. 4,925,673) and Kayyem et al. (U.S. Patent 6, 232, 295) does not produce the claimed invention and requests withdrawal of this rejection under 35 USC § 103(a).

Lohrmann, Steiner, Kayyem and Mathiowitz

Claims 3, 4, 10 and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lohrmann et al. (U.S. 6,193,953) in view of Steiner et al. (U.S. Patent 4,925,673), and Kayyem et al. (U.S. Patent 6, 232, 295), and further in view of Mathiowitz et al. (U.S. Patent 5,271,961).

According to the Examiner, Lohrmann et al., Steiner et al. and Kayyem differ from the instant invention in failing to teach that the proteinoid microsphere is formed by thermal condensation of amino acids in the presence of a cross linking agent. However, the Examiner

asserts that Mathiowitz discloses that protein microspheres can be modified by cross-linking agents such as glutaraldehyde.

Claims 3 and 4 depend from claim 1. Claim 3 states that the labeled proteinoid microsphere of claim 1 is formed by thermal condensation of the mixture of amino acids in the presence of a crosslinking agent such that the proteinoid microsphere further comprises a crosslinking agent. Claim 4 is directed to a labeled proteinoid microsphere of claim 3 wherein the crosslinking agent is carbodiimide, glutaraldehyde, N-(m-maleimidobenzoyloxy)-succinimide, a bifunctional sulfhydral reagent.

Claim 10 is directed to the labeled proteinoid microsphere of claim 7 wherein the proteinoid microsphere is formed by thermal condensation of a mixture of amino acids in the presence of a crosslinking agent such that the proteinoid microsphere further comprises a crosslinking agent. Claim 11 depends from claim 10 and identifies the crosslinking agents as carbodiimide, glutaraldehyde, N-(m-maleimidobenzoyloxy)-succinimide, a bifunctional sulfhydral reagent.

Mathiowitz (U.S. Patent No. 5,271,961) is limited to disclosure of methods for making protein microspheres by solvent evaporation of a solution of proteins (not amino acids). The Mathiowitz disclosure is also limited to attachment of a crosslinking agent prior to formation of the protein microspheres. Mathiowitz emphasizes that the protein microspheres are made under gentle conditions and teaches that the proteins are treated with crosslinking agent prior to formation of the protein microspheres. Applicant submits that if the teaching of Mathiowitz were followed, one would add the cross linker to the amino acids of Steiner before thermal condensation which would not necessarily yield the present proteinoid microspheres. Mere mention of a cross-linker in a reference does not mean that one of skill in the art would necessarily know how or why to use the cross-linking agent. There must be some teaching in the cited references to motivate one of skill in the art to make and use the invention as claimed.

Here, Steiner is the only reference that discloses anything about proteinoid microspheres. However, the microspheres of Steiner are specifically designed to be unstable under selected conditions so that the pharmacological agents encapsulated therein will be released.

Applicant submits that there is no motivation to modify the teachings of Steiner on unstable proteinoid microspheres by addition the crosslinking agent disclosed in Mathiowitz. If

a crosslinking agent were used to stabilize the proteinoid microspheres of Steiner, the very purpose of the Steiner microspheres would be defeated. Therefore, Steiner provides no motivation to the skilled artisan to identify and use an appropriate crosslinking agent.

Neither does Mathiowitz provide a motivation to employ the disclosed crosslinking agent on proteinoid microspheres. As described above, Mathiowitz is limited to a teaching on protein (not amino acid) microspheres. Mathiowitz contemplates making protein microspheres for controlled or target drug delivery (col. 2, lines 10-16) and does not disclose any reason to stabilize those protein microspheres by crosslinking. Moreover, Mathiowitz teaches away from using proteinoid microspheres (see, e.g., col. 1, lines 27-50) and provides no motivation to seek or use anything other than a protein microsphere. Instead, Mathiowitz teaches the benefits of using protein microspheres that require only mild conditions for their formation, thereby avoiding thermal degradation of the protein and the encapsulated drug (see, e.g., col. 1, lines 23-32).

Neither Lohrmann nor Kayyem cures this defect because nowhere does Lohrmann or Kayyem disclose proteinoid microspheres. Instead, Lohrmann and Kayyem are limited to teachings on proteins.

Therefore, Applicant submits that the combination of Lohrmann, Steiner, Kayyem and Mathiowitz would not motivate one of skill in the art to modify the teachings therein to find the present invention.

Moreover, one of skill in the art would not have a reasonable expectation of successfully producing Applicant's invention from the teachings of the cited references for several reasons. First, Mathiowitz explicitly states that any such crosslinking should not be done *during* microsphere formation (see Mathiowitz, claim 1). And, third, Mathiowitz provides no teaching that crosslinking of amino acids during thermal condensation can successfully produce a microsphere. Given that Lohrmann and Steiner fail to disclose that proteinoid microspheres would be sufficiently stable under a variety of pH and other conditions to retain an encapsulated label, and that Mathiowitz not only provides no methods for forming microspheres in the presence of crosslinking agents but actually states that one of skill should not form microspheres in the presence of a crosslinking agent, the skilled artisan could not reasonably expect to successfully make the present invention.

Therefore, Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953), Steiner (U.S. Patent No. 4,925,673), Kayyem et al. (U.S. Patent 6, 232, 295) and Mathiowitz (U.S. Patent 5,271,961) does not produce the claimed invention and requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 3, 4, 10 and 11.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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This paper or fee is being filed on the date indicated above using the USPTO's electronic filing system EFS-Web, and is addressed to: The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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